Remarks

Claims 1-138 are pending. Claims 137 and 138 were previously withdrawn from consideration as being drawn to a non-elected invention.

Rejection Under 35 U.S.C. § 103

Claims 1-136 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kingsmore et al. (U.S. Pat. No. 6,921,642) in view of Baner et al. (Nucleic Acids Res., Vol. 26, 922; pages 5073-5078 (1998)). Applicants respectfully traverse this rejection to the extent it applies to the claims as amended.

In making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a prima facie case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. See *In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. See *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office also has the burden under § 103 to establish a prima facie case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. See *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The present rejection does not meet this burden.

Claims 1, 107, 108, 110, 124, and 133-136, as well as all the claims dependent there from, are directed to methods of detecting one or more analytes. Each of the claims require specific compositions that interact together as well as a specific order in which each of the required interactions take place. Specifically, the claims require the use of reporter binding molecules. As claimed, the reporter binding molecules comprise a specific binding molecule and an amplification target circle. That is, the claimed reporter binding molecules specifically

include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the specific binding molecule. Only after the amplification target circle is decoupled from the specific binding molecule, is a rolling circle replication primer introduced and hybridized to the decoupled amplification target circle. Then, and only after the amplification target circle is decoupled from the specific binding molecule (which interacts with the analyte), is the amplification target circle replicated. In other words, the amplification target circle is not associated with the analyte-specific binding molecule composition when it is replicated. Thus, the claims require at least (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle associated with the analyte from that specific binding molecule, and (3) replication of the decoupled amplification target circle.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers. The reporter binding primers disclosed by Kingsmore et al. comprise a specific binding molecule and a rolling circle replication primer. The analytes are brought into contact with the reporter binding primers in such a way that the specific binding molecule binds to the analyte. Once the specific binding molecule of the reporter binding primer binds to the analyte, an amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. As such, the replication of the amplification target circle takes place in such a way that the amplification target circle remains associated with the analyte as it is replicated, thus the TS-DNA formed also remains associated with the analyte. Kingsmore et al. fails to teach or suggest the claimed reporter binding molecule (a combination of a specific binding molecule and an amplification target circle). Kinsgsmore et al. and also fails to teach or suggest decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al., the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with

the reporter binding primer during replication (see the bottom panels of Figure 1 where the amplification target circle is shown at the growing tip of the replicated strand as well as Figures 11, 13 and 14). Applicants further submit that Kingsmore et al. teaches away from such a method of detection, specifically Kingsmore et al. teaches away from decoupling of the amplification target circle from the specific binding molecules prior to replication of the amplification target circle.

Baner et al. discloses padlock probes and their potential uses to detect sets of gene sequences with high specificity and selectivity for sequence variants. In order for the reaction of Baner et al. to take place, the linear oligonucleotides (un-circularized padlock probes) must first hybridize to their target, then, if properly hybridized, the 5' and 3' ends of the linear oligonucleotides can be joined by enzymatic ligation, thus converting the probes into circularly closed molecules that are concatenated to the target. The circularly closed molecules (padlock probes) can then be subjected to rolling circle replication. Baner et al. also discloses that to increase the efficiency of the rolling circle replication of the padlock probes, the topological link formed between the padlock probe and its target sequence can be removed, however, the methods disclosed by Baner et al. all require initiation of rolling circle replication prior to the release of the padlock probe from the target sequence. In other words, the rolling circle replication primer was hybridized to the padlock probe prior to release of the padlock probe from its target sequence. Baner et al. fails to disclose or suggest a reporter binding molecule comprising a specific binding molecule and an amplification target circle. Applicants further submit that Baner et al. fails to disclose or suggest the decoupling of amplification target circles from their associated specific binding molecules prior to replication of the amplification target circles.

As claimed, the reporter binding molecules comprise a specific binding molecule and an amplification target circle. That is, the claimed reporter binding molecules include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the reporter binding molecule. The decoupled amplification target circle is then replicated. Thus, the claims require at least (1) a

reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle from that reporter binding molecule, and (3) replication of the decoupled amplification target circle. .

The Office Action appears to equate materials disclosed Kingsmore et al.; alleging that they correspond to certain claimed materials. In particular, the rejection appears to equate (page 3, lines 7-8) the reporter binding primers of Kingsmore et al. with the claimed reporter binding molecules. This is simply wrong. Although the reporter binding primers disclosed in Kingsmore et al. do comprise a specific binding molecule, they do not comprise an amplification target circle as claimed. The reporter binding primers of Kingsmore et al. comprise a specific binding molecule and a rolling circle replication primer (see column 41, lines 50-52). A rolling circle replication primer is not the same as an amplification target circle. A rolling circle replication primer and an amplification target circle are very different in form and function. Applicants believe the equation of the two molecules was simply an oversight of the Examiner and do not deem it necessary to go into the specific form and functional differences at this time.

Applicants do believe the differences to be relevant, especially in that the timing of the addition of each of the components is relevant to the claimed methods. Specifically, as stated above, the claims require specific compositions that interact together as well as a specific order in which each of the required interactions take place. Only after the amplification target circle is decoupled from the specific binding molecule, is a rolling circle replication primer introduced and hybridized to the decoupled amplification target circle. As such, Applicants further submit that Kingsmore et al. also fails to teach (1) decoupling of the amplification target circle associated with the analyte from the specific binding molecule, and (2) bringing into contact a rolling circle replication primer and the amplification target circles only after the decoupling of the amplification target circles associated with the analyte from the specific binding molecule (see Claim 1, step (c); Claim 107, step (d); Claim 108, step (d); and Claim 110, step (d)).

The Office Action admits (Page 7, lines 8-9) that Kingsmore et al. fails to disclose a decoupling step to dissociate the amplification target circle associated with analytes from specific binding molecules. Applicants do not take issue with the Office Action's assertion.

Applicants further assert that not only does Kingsmore et al. fail to specifically disclose or suggest such a step, but in fact, Kingsmore et al. actually teaches away from such a proposition. Kingsmore et al. specifically provides that the amplified DNA (the TS-DNA from the rolling circle replication of the amplification target circles) remains associated with the analyte, via the primer, and so allows spatial detection of the analyte (see abstract and column 4, lines 55-57). Figures 1, 11, 13 and 14 further illustrate the teaching away, where each of the reactions are carried out with the amplification target circle attached to the rolling circle replication primer-specific binding molecule (replication binding primer) which is associated with the anaytle during the replication reaction. In other words, Kingsmore et al. requires that the amplification target circle to NOT be decoupled from the specific binding molecule. Nowhere in Kingsmore et al. is any other method or system taught or suggested. The Office Action's reliance on Figure 1 for teaching or suggesting such a limitation is therefore incorrect.

Baner et al. which was cited for teaching releasing a padlock probe the link that forms with target molecules upon hybridization and ligation, fails to supplement the missing elements from Kingsmore et al. Specifically, Baner *et al.* fails to teach or suggest (1) a reporter binding molecule that comprises both a specific binding molecule (that can interact with an analyte) and an amplification target circle and (2) decoupling of that amplification target circle associated with the analyte from that specific binding molecule, and (3) replication of the decoupled amplification target circle. In fact, Applicants submit that the Office Action does not cite Baner et al. for teaching or suggesting the claimed reporter binding molecules. Applicants therefore submit that Kingsmore et al. and Baner et al. fail to teach or suggest a reporter binding molecule that comprises both a specific binding molecule (that can interact with an analyte) and an amplification target circle As such, Applicants further submit that Kingsmore et al. and Baner et al., either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, Kingsmore et al. and Baner et al. fail to make obvious claims 1-136.

Applicants further submit that it is only logical to deduct that since Baner et al. fails to teach an amplification target circle coupled with a specific binding molecule, that it is impossible to teach decoupling of an amplification target circle coupled from a specific binding molecule as

required by the claims. In other words, if the compositions are not taught by either of the two cited references, thus neither of the two cited references could teach a specific interaction of the non-disclosed compositions.

The Office Action (page 7, lines 10-18) appears to rely on Baner et al. for teaching the missing step of decoupling of the amplification target circles associated with the analyte from the specific binding molecule. Aside from the failure of either Kingsmore et al. or Baner et al. to teach or suggest the claimed reporter binding molecules, Baner et al. fails to teach bringing into contact a rolling circle replication primer and the amplification target circles only after the decoupling of the amplification target circles associated with the analyte from the specific binding molecule (see Claim 1, step (c); Claim 107, step (d); Claim 108, step (d); and Claim 110, step (d)). As described above, Baner et al. discloses padlock probes and their potential uses to detect sets of gene sequences with high specificity and selectivity for sequence variants. In order for the reaction of Baner et al. to take place, the linear oligonucleotides (un-circularized padlock probes) must first hybridize to their target, then, if properly hybridized, the 5' and 3' ends of the linear oligonucleotides can be joined by enzymatic ligation, thus converting the probes into circularly closed molecules that are concatenated to the target. The circularly closed molecules (padlock probes) can then be subjected to rolling circle replication. In the methods described by Baner et al. (see page 5074, column 1 and 2 under "Conditions for radiolabeling, ligation, polymeration and restriction digestion") once the ligation reaction has taken place, the rolling circle replication primer (P1) is added to a reaction mixture with the Φ29 DNA polymerase and other components prior to the incubation step that allows rolling circle replication to take place. What Baner et al. goes on to discuss is the ability of the ligated padlock probe to dissociate from the target when the Φ29 DNA polymerase begins to extend the rolling circle replication primer. Because of the polymerase's ability to remove the 3' non-probe-complementary nucleotides from the target (see page 5076, column 1, first full sentence) the padlock probe can be released from the target and by doing so, the efficiency of the rolling circle replication of the amplification target circle is allowed to progress. In other words, the rolling circle replication primer is added to the mixture and subsequently hybridized to the amplification target circle before the release of the amplification target circle from the target sequence. In fact, the rolling

circle replication primer must be hybridized and the rolling circle replication reaction must take place prior to the dissociation of the amplification target circle from the target according to Baner et al. As such, Baner et al. fails to teach or suggest bringing into contact a rolling circle replication primer and the amplification target circles only after the decoupling of the amplification target circles associated with the analyte from the specific binding molecule. Furthermore, Baner et al. teaches away from such a reaction as described above.

Even if, one of skill in the art were to accept the Office Action's allegation that Baner et al. teaches decoupling of an amplification target circles associated with an analyte from the specific binding molecule associated with the same analyte, Applicant's submit that it would not be obvious to one of ordinary skill in the art to combine such a teaching with the teachings of Kingsmore et al. The Office Action alleges (page 8, lines 1-6) that one of skill in the art would have been motivated to combine Baner et al. and Kingsmore et al. based on Baner et al.'s alleged teaching of using circularized probes to yield a powerful signal amplification by releasing the link that forms between the circular probe and the target sequence (which Applicants rebut above). Applicants reject the Office Action's allegation and submit that one of ordinary skill in the art would not have been motivated to combine the references of Kingsmore et al. and Baner et al. as suggested by the Office Action because (1) modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and (2) Kingsmore et al. teaches away from decoupling of the amplification target circle from the specific binding molecules prior to replication of the amplification target circle and thus the present rejection cannot be sustained.

A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

As provided above, Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule

binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. In the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

In fact, if the amplification target circle was dissociated from the reporter binding primer prior to replication, as suggested by the Office Action, the amplification target circle could not be replicated because such dissociation would separate the amplification target circle from the rolling circle replication primer (the primer is part of the reporter binding primer). Further, even if such a hypothetical dissociated amplification target circle was replicated using a different primer, this would defeat Kingsmore et al.'s purpose in having a rolling circle replication primer as part of a reporter binding primer. Kingsmore et al. states that:

> The method involves associating nucleic acid primer with the analyte and subsequently using the primer to mediate rolling circle replication of a circular DNA molecule. Amplification of the DNA circle is dependent on the presence of the primer. Thus, the disclosed method produces an amplified signal, via rolling circle amplification, from any analyte of interest. The amplification is isothermic and can result in the production of a large amount of nucleic acid from each primer. The amplified DNA remains associated with the analyte, via the primer, and so allows spatial detection of the analyte.

Column 4, lines 37-47 (emphasis added).

Dissociation of the amplification target circle would eliminate the intended connection between the analyte and the amplified DNA and thus eliminate the spatial detection of the analyte sought by Kingsmore et al. This alteration, required by the present rejection, would eliminate a major feature of the method of Kingsmore et al. Such a change in the principle of operation of the method of Kingsmore et al., which results from the modification proposed by the rejection, renders the rejection unsustainable. Furthermore, the above cited portions of Kingsmore et al. establish that Kingsmore et al. teaches away from decoupling of the amplification target circle from the specific binding molecules prior to replication of the

amplification target circle. Such a teaching away would not lead or motivate one of ordinary skill in the art to combine the methods of Kingsmore et al. with the alleged teaching of Baner et al. Accordingly, Kingsmore et al. and Baner et al. fail to make obvious the method of claims 1-136.

For all the reasons above, Kingsmore et al. and Baner et al., either alone or in combination, fail to disclose or suggest every feature of the claims. In addition, one of ordinary skill in the art would not be motivated to combine Kingsmore et al. and Baner et al. because such a combination would alter the fundamental principle of operation of Kingsmore et al. as well as the fact that Kingsmore et al. teaches away from such a combination. Accordingly, Kingsmore et al. and Baner et al. fail to make obvious claims 1-136.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card payment in the amount of $230.00, representing $230.00 for the extension of time fee for a small entity under 37 C.F.R. § 1.17(a)(2) and a Request for Two Month Extension of Time are also enclosed. This amount is believed to be correct; however, the

Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Scott D. Marty
Registration No. 53,277

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

Scott D. Marty

11-15-07
Date